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(54) Process for the manufacture of substituted maleimides

Verfahren zur Herstellung substituierter Maleimide

Procédé de fabrication de maléimides substitués

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- **JOURNAL OF THE AMERICAN CHEMICAL SOCIETY vol. 70, 1948, pages 4011 - 4013; G.S. SKINNER ET AL.: 'The Reaction of Bromine with Arylcyanopyruvic Esters'**
- **TETRAHEDRON LETTERS vol. 31, no. 36, 1990, pages 5201 - 5204; P.D. DAVIS, R.A. BIT: 'A Mild Conversion of Maleic Anhydrides into Maleimides'**

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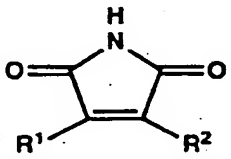
Description

The present invention relates to a process for the manufacture of substituted maleimides.

More particularly, the invention is concerned with a process for the manufacture of 2-substituted and 2,3-disubstituted maleimides of the general formula



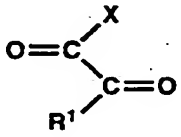
(I)

wherein R^1 represents alkyl, aryl or heteroaryl and R^2 represents hydrogen, alkyl, alkoxycarbonyl, cycloalkyl, aryl or heteroaryl.

The substituted maleimides of formula I hereinbefore have valuable pharmacological properties. For example, they are protein kinase C (PKC) inhibitors as described e.g. in US 5057614, EPA 0384349 and EPA 0470490 or antiproliferative agents as described e.g. in DE 4005970.

As used herein, the term 'alkyl' means a straight-chain or branched-chain alkyl group which preferably contains a maximum of 8 carbon atoms, e.g. methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert.butyl, pentyl, hexyl, heptyl etc. The term 'alkoxy- carbonyl' means a straight-chain or branched-chain alkoxy- carbonyl group which preferably contains a maximum of 8 carbon atoms in the alkoxy group, e.g. methoxycarbonyl, ethoxycarbonyl, isopropoxycarbonyl etc. The term 'cycloalkyl' means a cycloalkyl group which preferably contains from 3 to 8 carbon atoms and which can be optionally substituted, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl etc. The term 'aryl' means an optionally substituted monocyclic, bicyclic or polycyclic aromatic ring, e.g. phenyl, naphthyl, anthryl, phenanthryl etc. The term 'heteroaryl' means an optionally substituted monocyclic, bicyclic or poly- cyclic aromatic ring in which one or more carbon atoms has been replaced by one or more nitrogen, oxygen and/or sulphur atoms, e.g. pyridyl, thienyl, indolyl, benzothiophenyl etc.

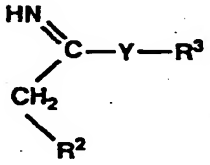
According to the invention the substituted maleimides of formula I hereinbefore are manufactured by reacting an activated glyoxylate of the general formula



(II)

wherein R^1 has the significance given earlier and X represents a leaving atom or group,

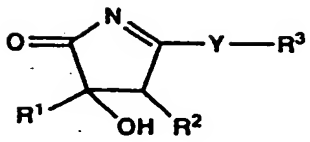
with an imidate of the general formula



(III)

wherein R^2 has the significance given earlier, R^3 represents alkyl, aryl or trialkylsilyl and Y represents oxygen or sulphur,

in the presence of a base and, after treating a reaction product obtained in which R^2 represents hydrogen or alkyl with a strong base, hydrolyzing and dehydrating the resulting hydroxy-pyrrolinone of the general formula



(IV)

wherein R^1, R^2, R^3 and Y have the significance given earlier.

The leaving atom or group denoted by X in an activated glyoxylate of formula II can be, e.g. a halogen atom such as chlorine, an alkoxycarbonyloxy group, e.g. methoxycarbonyloxy, ethoxycarbonyloxy, isopropoxycarbonyloxy etc., the pentafluorophenoxy group, or the like. In a preferred embodiment, X represents a halogen atom, especially chlorine.

The reaction of an activated glyoxylate of formula II with an imidate of formula III is conveniently carried out in an organic solvent which is inert under the conditions of the reaction. Suitable bases are, for example, tertiary amines, e. g. triethylamine, diisopropylethylamine, 4-dimethylaminopyridine, N-ethylmorpholine, 1,4-diazabicyclo[2,2,2]octane etc, pyridine and the like. Suitable solvents are, for example, halogenated aliphatic hydrocarbons, e.g. dichloromethane, chloroform etc., optionally halogenated aromatic hydrocarbons, e.g. benzene, toluene, chlorobenzene etc., open-chain and cyclic ethers, e.g. dimethoxyethane, tert.butyl methyl ether, tetrahydrofuran etc., formamides, e.g. dimethylformamide etc., esters, e.g. ethyl acetate etc. and nitriles, e.g. acetonitrile etc. The reaction is preferably carried out at about 0°C to about 40°C, especially at about room temperature.

When a substituted glyoxylate of formula II in which R^2 represents hydrogen or alkyl is used, the reaction product obtained must be treated with a strong base. Especially suitable strong bases are alkali metal alkoxides, particularly potassium tert.butoxide.

The hydrolysis and dehydration of a hydroxy-pyrrolinone of formula IV to give a substituted maleimide of formula I is expediently carried out by treatment with a mineral acid, e.g. hydrochloric acid, sulphuric acid etc., or an organic acid, e.g. methanesulphonic acid, p-toluenesulphonic acid etc., or by treatment with an acylating reagent, e.g. trifluoroacetic anhydride, and a suitable base; e.g. pyridine, conveniently at about room temperature. The hydroxy-pyrrolinone of formula IV is preferably hydrolyzed and dehydrated in situ; that is to say, the process is preferably carried out as a so-called "one-pot" process.

The activated glyoxylate starting materials of formula II are known compounds or analogues of known compounds which can be prepared in analogy to the known compounds or as described in the following Examples or in analogy thereto.

The imidate starting materials of formual III, insofar as they are not known compounds or analogues of known compounds, can be prepared by reacting a nitrile of the general formula

$$R^2\text{-}CH_2\text{-}CN \qquad (V)$$

wherein R^2 has the significance given earlier,
with a compound of the general formula

$$H\text{-}Y\text{-}R^3 \qquad (VI)$$

wherein R^3 has the significance given earlier.
The reaction is carried out in a known manner, e.g. in the presence of hydrogen chloride.

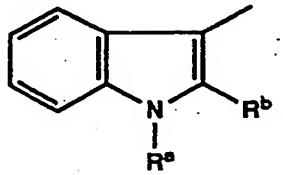
Alternatively, imidate starting materials of formula III in which R^3 represents trialkylsilyl and Y represents oxygen can be prepared by reacting an amide of the general formula

$$R^2\text{-}CH_2\text{-}CONH_2 \qquad (VII)$$

wherein R^2 has the significance given earlier,
with a halotrialkylsilane, e.g. chlorotrimethylsilane, in the presence of triethylamine. The reaction is carried out in a known manner, for example in a solvent which is inert under the reaction conditions, e.g. a halogenated hydrocarbon such as dichloromethane etc, and at about room temperature.

Preferred activated glyoxylate starting materials of formula II are those in which R^1 represents optionally substituted

phenyl, naphthyl, thienyl, benzothiophenyl or indolyl, especially a 3-indolyl group of the general formula



(a)

wherein R^a represents alkyl, particularly methyl, or alkanoyl, particularly acetyl, and R^b represents hydrogen or alkyl, particularly methyl, or R^a and R^b together represent a tetramethylene group optionally substituted by acyloxyalkyl, particularly acetoxymethyl.

Preferred imidate starting materials of formula III are those in which R^2 represents optionally substituted indolyl, especially 3-indolyl or 1-alkyl-3-indolyl, particularly 1-methyl-3-indolyl, and R^3 represents secondary alkyl, especially isopropyl.

As mentioned earlier, the substituted maleimides of formula I are, for example, protein kinase C inhibitors, which can be used e.g. in the treatment and prophylaxis of inflammatory, immunological, bronchopulmonary and cardiovascular disorders, or antiproliferative agents, which can be used e.g. in the treatment of immune diseases and allergic disorders. The present invention enables these substituted maleimides to be manufactured in good yields and purity starting from readily accessible starting materials.

The following Examples illustrate the present invention.

Example 1

A solution of 235 mg (1 mmol) of 1,2-dimethylindole-3-glyoxylyl chloride in 20 ml of dry dichloromethane was added dropwise to a solution of 266 mg (1 mmol) of isopropyl 1-methyl-3-indoleacetimidate hydrochloride and 404 mg (4 mmol) of triethylamine in 20 ml of dry dichloromethane containing 4Å molecular sieves. On completion of the addition the mixture was stirred at room temperature under nitrogen for 18 hours. 950 mg (5 mmol) of p-toluenesulphonic acid were then added and stirring was continued for 1 hour. The mixture was filtered, the filtrate was evaporated to dryness and the residue was purified by flash chromatography on silica gel using dichloromethane/ ethyl acetate (8:1) for the elution. There were obtained 257 mg (70%) of 3-(1,2-dimethyl-3-indolyl)-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione in the form of a red solid of melting point >290°C.

The isopropyl 1-methyl-3-indoleacetimidate hydrochloride used as the starting material was prepared as follows:

Hydrogen chloride was bubbled through a stirred solution of 7.5 g (44 mmol) of 1-methylindole-3-acetonitrile in 100 ml of dry isopropanol at room temperature. After 4 hours the solvent was removed under reduced pressure and the residue was triturated with diethyl ether to give 5.17 g (44%) of isopropyl 1-methyl-3-indoleacetimidate hydrochloride as a white solid of melting point 133°C.

Example 2

A stirred solution of 10 g (41 mmol) of (S)-8-(acetoxy-methyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole in 100 ml of dichloromethane was treated dropwise at 0°C with 4.3 ml (49 mmol) of oxalyl chloride. After 5 minutes the solvent was removed by evaporation under reduced pressure and the residue was suspended in 150 ml of toluene and treated with 9.5 g (41 mmol) of isopropyl 1-methyl-3-indoleacetimidate hydrochloride (prepared as described in Example 1). The stirred suspension was cooled to 0°C and treated dropwise with 23 ml (166 mmol) of triethylamine. After stirring for 18 hours at room temperature under nitrogen the thick suspension was partitioned between dichloromethane, toluene and 0.5M hydrochloric acid. The organic extracts were dried over sodium sulphate, filtered and treated with a suspension of 15.6 g (82 mmol) of p-toluenesulphonic acid in 100 ml of toluene. The mixture was stirred at room temperature for 2.5 hours, washed with water, saturated sodium bicarbonate solution and brine, dried over sodium sulphate and evaporated to give a brown solid. Trituration with diethyl ether gave 13.73 g 72% of (S)-3-[8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indol-10-yl]-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione. A sample was crystallized from dichloromethane/ methanol to give an orange solid of melting point 238-241°C.

The (S)-8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole used as the starting material was prepared as follows:

A mixture of 4.47 g (20.8 mmol) of 6,7,8,9-tetrahydropyrido[1,2-a]indole-8-carboxylic acid and 3.9 g (25 mmol) of 1-menthol in 100 ml of dichloromethane was treated with 0.25 g (2.05 mmol) of 4-dimethylaminopyridine and cooled in ice. 6.08 g (22.9 mmol) of dicyclohexylcarbodiimide in 20 ml of dichloromethane were added dropwise during 10

minutes. After 0.5 hour the suspension was filtered through a pad of diatomaceous earth and the filtrate was evaporated. Flash chromatography (diethyl ether/hexane, 1:5) gave 6.09 g (83%) of mixed diastereoisomers as an oil. The isomers were separated either by flash chromatography on silica gel using diethyl ether/hexane (1:9) for the elution or by fractional crystallization from isopropanol. Menthyl 6,7,8,9-tetrahydropyrido[1,2-a]indole-8(S)-carboxylate melted at 117-118°C and had the rotation $[\alpha]_{589}^{20} = -76.2°$ (c = % in chloroform). The corresponding (R) isomer melted at 87-89°C and had the rotation = -22.8° (c = 1% in chloroform).

A solution of 0.8 g (2.27 mmol) of 1-menthyl 6,7,8,9-tetrahydropyrido[1,2-a]indole-8(S)-carboxylate in 15 ml of dry tetrahydrofuran was treated dropwise under a nitrogen atmosphere with 2 ml (2 mmol) of 1M lithium aluminium hydride. After 10 minutes the mixture was cooled in ice, treated successively with 5 ml of ethyl acetate and 30 ml of water and acidified with 1M hydrochloric acid. The mixture was extracted three times with diethyl ether and the combined extracts were dried over sodium sulphate and evaporated. Flash chromatography on silica gel using ethyl acetate/hexane (1:1) for the elution gave (S)-8-(hydroxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole as a white solid which was dissolved in 5 ml of dichloromethane. 0.43 g (4.21 mmol) of acetic anhydride and 0.9 ml (6.5 mmol) of triethylamine were added and the solution was left to stand for 17 hours. The solvent was evaporated and the residue was partitioned between 5% aqueous sodium bicarbonate solution and diethyl ether. The organic phase was dried over sodium sulphate and evaporated, and the residue was crystallized from aqueous ethanol to give 0.518 g (94%) of (S)-8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole as a white solid of melting point 63-64°C; $[\alpha]_{589}^{20} = -43.7°$ (c = 1% in chloroform).

Example 3

In a manner analogous to that described in Example 1, from 222 mg (1 mmol) of 1-methylindole-3-glyoxylyl chloride and 213 mg (1 mmol) of isopropyl phenylacetamidate hydrochloride there were obtained 185 mg (61%) of 3-(1-methyl-3-indolyl)-4-phenyl-1H-pyrrole-2,5-dione in the form of an orange solid of melting point 230-232°C.

Example 4

In a manner analogous to that described in Example 1, from 222 mg (1 mmol) of 1-methylindole-3-glyoxylyl chloride and 263 mg (1 mmol) of isopropyl 2-napthaleneacetimidate hydrochloride there were obtained 174 mg (49%) of 3-(1-methyl-3-indolyl)-4-(2-naphthyl)-1H-pyrrole-2,5-dione in the form of an orange solid of melting point 269-271°C.

The isopropyl 2-naphthaleneacetimidate hydrochloride used as the starting material was prepared in a manner analogous to that described in Example 1 from 2-naphthylacetonitrile. It was obtained in the form of a white solid of melting point 180-184°C.

Example 5

In a manner analogous to that described in Example 1, from 222 mg (1 mmol) of 1-methylindole-3-glyoxylyl chloride and 269 mg (1 mmol) of isopropyl 3-benzothiopheneacetimidate hydrochloride there were obtained 196 mg (55%) of 3-(1-benzothiophen-3-yl)-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione as an orange solid of melting point 238-241°C.

The isopropyl 3-benzothiopheneacetimidate hydrochloride used as the starting material was prepared as follows:

In a manner analogous to that described in Example 1, from benzothiophene-3-acetonitrile there was obtained isopropyl 3-benzothiopheneacetimidate hydrochloride as a cream coloured solid of melting point 93-95°C.

Example 6

In a manner analogous to that described in Example 1, from 222 mg (1 mmol) of 1-methylindole-3-glyoxylyl chloride and 294 mg (1 mmol) of isopropyl 1-acetyl-3-indoleacetimidate hydrochloride there were obtained 184 mg (48%) of 3-(1-acetyl-3-indolyl)-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione in the form of a red solid of melting point 252-253°C.

The isopropyl 1-acetyl-3-indoleacetimidate hydrochloride used as the starting material was prepared as follows:

In a manner analogous to that described in Example 1, from 1-acetylindole-3-acetonitrile there was obtained isopropyl 1-acetyl-3-indoleacetimidate hydrochloride in the form of a white solid of melting point 122-125°C.

Example 7

In a manner analogous to that described in Example 1, from 222 mg (1 mmol) of 1-methylindole-3-glyoxylyl chloride and 225 mg (1 mmol) of isopropyl 3-thiopheneacetimidate hydrochloride there were obtained 105 mg (58%) of 3-(1-methyl-3-indolyl)-4-(3-thienyl)-1H-pyrrole-2,5-dione in the form of an orange coloured solid of melting point 225-227°C.

The isopropyl 3-thiopheneacetimidate hydrochloride used as the starting material was prepared as follows:

In a manner analogous to that described in Example 1, from 3-thiopheneacetonitrile there was obtained isopropyl 3-thiopheneacetimidate hydrochloride in the form of a beige solid of melting point 118-119°C.

Example 8

In a manner analogous to that described in Example 1, from 222 mg (1 mmol) of 1-methylindole-3-glyoxylyl chloride and 225 mg (1 mmol) of isopropyl 3-imino-3-isopropoxypropionate hydrochloride there were obtained 71 mg (23%) of 3-(isopropoxycarbonyl)-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione in the form of an orange coloured solid of melting point 199-202°C.

The isopropyl 3-imino-3-isopropoxypropionate hydrochloride used as the starting material was prepared as follows:

In a manner analogous to that described in Example 1, from isopropyl 2-cyanoacetate there was obtained isopropyl 3-imino-3-isopropoxypropionate hydrochloride in the form of a beige solid of melting point 73-75°C.

Example 9

165 mg (1.38 mmol) of oxalyl chloride were added to a stirred solution of 300 mg (1.24 mmol) of 8-acetoxymethyl-6,7,8,9-tetrahydropyrido[1,2-a]indole in 50 ml of dichloromethane at 0°C. The resulting solution was stirred for 15 minutes and the solvent was removed by evaporation. The residue was dissolved in 30 ml of toluene and added dropwise to a stirred solution of 496 mg (4.96 mmol) of triethylamine and 331 mg (1.31 mmol) of isopropyl 3-indoleacetimidate hydrochloride in 20 ml of toluene. After 18 hours 1.16 g (6.2 mmol) of p-toluenesulphonic acid were added and stirring was continued for 1 hour. The mixture was then partitioned between dichloromethane and water. The organic phase was dried over sodium sulphate and evaporated to dryness. The residue was purified by flash chromatography on silica gel using ethyl acetate/petroleum ether (1:1) for the elution to give 170 mg (38%) of 3-[8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indol-10-yl]-4-[3-indolyl)-1H-pyrrole-2,5-dione in the form of an orange coloured solid of melting point 264-265°C.

The isopropyl 3-indoleacetimidate hydrochloride used as the starting material was prepared as follows:

In a manner analogous to that described in Example 1, from indole-3-acetonitrile there was obtained isopropyl 3-indole-acetimidate hydrochloride as a beige solid of melting point 132-134°C.

Example 10

A stirred solution of 406 mg (2 mmol) of 1-methyl-3-indolylglyoxylic acid in 20 ml of dichloromethane was treated with 202 mg (2 mmol) of triethylamine and 273 mg (2 mmol) of isobutyl chloroformate. After 0.5 hour the solution was added dropwise to a stirred solution of 533 mg (2 mmol) of isopropyl 1-methyl-3-indoleacetimidate hydrochloride and 808 mg (8 mmol) of triethylamine in 50 ml of dichloromethane. The solution obtained was heated to reflux under nitrogen for 18 hours, cooled and treated with 1.9 g (10 mmol) of p-toluene-sulphonic acid. After 1 hour the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using dichloromethane/ethyl acetate (8:1) for the elution to give 107 mg (30%) of 3,4-bis-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione in the form of an orange coloured solid of melting point >310°C.

Example 11

A stirred solution of 1.0 g (7.6 mmol) of 1-methylindole in 25 ml of diethyl ether was treated at 0°C under a nitrogen atmosphere with 1.81 g (8.4 mmol) of oxalyl bromide. After 1 hour the brown-red solid was filtered off and dried to give 1.2 g of 1-methylindole-3-glyoxylyl bromide. A solution of 266 mg (1 mmol) of this bromide in 25 ml of dichloromethane was added dropwise to a stirred solution of 266 mg (1 mmol) of isopropyl 1-methyl-3-indoleacetimidate hydrochloride and 404 mg (4 mmol) of triethylamine in 25 ml of dry dichloromethane. After 18 hours 950 mg (5 mmol) of p-toluenesulphonic acid were added and the mixture was stirred for 1 hour. The solvent was removed under reduced pressure and the residue was purified on silica gel using dichloromethane/ethyl acetate (8:1) for the elution to give 136 mg (38%) of 3,4-bis-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione as a red solid of melting point >310°C.

Example 12

In a manner analogous to that described in Example 1 from 222 mg (1 mmol) of 1-methylindole-3-glyoxylyl chloride and 283 mg (1 mmol) of isopropyl 1-methyl-3-indolethioacetimidate hydrochloride there were obtained 246 mg (69%) of 3,4-bis-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione as a red solid of melting point >300°C.

The isopropyl 1-methyl-3-indolethioacetimidate hydrochloride used as the starting material was prepared as follows:

Hydrogen chloride was bubbled through a stirred solution of 3 g (17.6 mmol) of 1-methylindole-3-acetonitrile and 6.7 g (88 mmol) of 2-propanethiol in 70 ml of dry diethyl ether for 2 hours. The mixture was left to stand for 3 days and then diluted with diethyl ether. The ether was decanted off and the residual gum was triturated with diethyl ether to give 3.76 g (87%) of isopropyl 1-methyl-3-indolethioacetimidate hydrochloride in the form of a grey solid of melting point 150°C.

Example 13

In a manner analogous to that described in Example 1, from 222 mg (1 mmol) of 1-methylindole-3-glyoxylyl chloride and 301 mg (1 mmol) of phenyl 1-methyl-3-indoleacetimidate hydrochloride there were obtained 35 mg (10%) of 3,4-bis-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione in the form of a red solid of melting point >300°C,

The phenyl 1-methyl-3-indoleacetimidate hydrochloride used as the starting material was prepared as follows:

Hydrogen chloride was bubbled through a solution of 3 g (176 mmol) of 1-methylindole-3-acetonitrile and 8.28 g (88 mmol) of phenol in 70 ml of dry diethyl ether for 2 hours and the resulting solution was left to stand for 4 days. The solvent was removed under reduced pressure and the residual gum was triturated with diethyl ether to give 1.4 g (30%) of 1-methyl-3-indoleacetimidate hydrochloride in the form of a purple solid of melting point 119°C.

Example 14

A solution of 222 mg (1 mmol) of 1 -methylindole-3-glyoxylyl chloride in 25 ml of dichloromethane was added dropwise to a stirred solution of 138 mg (1 mmol) of isopropyl ethanimidate hydrochloride and 404 mg (4 mmol) of triethylamine in 25 ml of dry dichloromethane under a nitrogen atmosphere. After 18 hours the mixture was washed twice with water, dried over sodium sulphate and evaporated under reduced pressure. The residue was dissolved in 25 ml of dry toluene under a nitrogen atmosphere and the solution obtained was treated with 112 mg (1 mmol) of potassium tert.butoxide. After stirring for 1 hour at room temperature 380 mg (2 mmol) of p-toluenesulphonic acid were added and stirring was continued for a further 1 hour. The mixture was then poured into water and extracted three times with dichloromethane. The combined organic extracts were dried over sodium sulphate and evaporated to dryness. The residue was purified by flash chromatography on silica gel using dichloromethane/ethyl acetate (9:1) for the elution to give 102 mg (45%) of 3-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione in the form of a yellow solid of melting point 229-231°C.

Example 15

In a manner analogous to that described in Example 14, from 222 mg (1 mmol) of 1-methylindole-3-glyoxylyl chloride and 361 mg (1 mmol) of isopropyl stearimidate hydrochloride there were obtained 289 mg (64%) of 3-(1-hexadecyl)-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione as a yellow solid of melting point 112-114°C.

The isopropyl stearimidate hydrochloride used as the starting material was prepared as follows:

In a manner analogous to that described in Example 1, from stearonitrile there was obtained isopropyl stearimidate hydrochloride as a white solid of melting point 54-55°C.

Example 16

A solution of 369 mg (1 mmol) of pentafluorophenyl 1-methylindole-3-glyoxylate in 20 ml of dichloromethane was added to a stirred solution of 266 mg (1 mmol) of isopropyl 1-methyl-3-indoleacetimidate hydrochloride and 404 mg (4 mmol) of triethylamine in 25 ml of dichloromethane. The solution obtained was heated to reflux under nitrogen for 18 hours, cooled and treated with 950 mg (5 mmol) of p-toluenesulphonic acid. After 1 hour the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using dichloromethane/ethyl acetate (8:1) for the elution to give 159 mg (45%) of 3,4-bis-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione in the form of an orange coloured solid of melting point >310°C.

The pentafluorophenyl 1-methylindole-3-glyoxylate used as the starting material was prepared as follows:

1.13 g (5.5 mol) of dicyclohexylcarbodiimide were added to a solution, cooled in ice, of 1 g (5 mmol) of 1-methylindole-3-glyoxylic acid and 1.01 g (5 mmol) of pentafluorophenol in 50 ml of dry tetrahydrofuran. After stirring for 4 hours under a nitrogen atmosphere at 0°C the mixture was allowed to warm to room temperature and then left to stand for 60 hours. 3 ml of glacial acetic acid were then added and the mixture obtained was filtered. The filtrate was concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel using dichloromethane for the elution to give 404 mg (22%) of pentafluorophenyl 1-methylindole-3-glyoxylate in the form of a pale yellow solid of melting point 168-9°C.

Example 17

In a manner analogous to that described in Example 14, from 222 mg (1 mmol) of 1-methylindole-3-glyoxlyl chloride and 220 mg (1 mmol) of isopropyl cyclohexylacetimidate hydrochloride there were obtained 109 mg (37%) of 3-cyclohexyl-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione in the form of a yellow solid of melting point 224-225°C.

The isopropyl cyclohexylacetimidate hydrochloride used as the starting material was prepared as follows:

In a manner analogous to that described in Example 1, from cyclohexylacetonitrile there was obtained isopropyl cyclohexylacetimidate hydrochloride in the form of a pale pink solid of melting point 108-110°C.

Example 18

109 mg (1 mmol) of chlorotrimethylsilane were added to a stirred solution of 188 mg (1 mmol) of 1-methylindole-3-acetamide and 110 mg (1.1 mmol) of triethylamine in 25 ml of dry dichloromethane. After 0.5 hour at room temperature a further 202 mg (2 mmol) of triethylamine were added, followed by a solution of 222 mg (1 mmol) of 1-methylindole-3-glyoxylyl chloride in 25 ml of dry dichloromethane. After completion of the addition the mixture obtained was stirred at room temperature for 18 hours. 950 mg (5 mmol) of p-toluenesulphonic acid were then added and stirring was continued for 1 hour. The solvent was evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel using dichloromethane/ethyl acetate (8:1) for the elution to give 49 mg of (14%) 3,4-bis-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione as a red solid of melting point 304-307°C

Example 19

A solution of 802 mg of pentafluorophenyl pyruvate in 20 ml of dichloromethane was added dropwise to a solution of 266 mg (1 mmol) of isopropyl 1-methyl-3-indoleacetimidate hydrochloride and 808 mg (8 mmol) of triethylamine in 20 ml of dichloromethane. After completion of the addition the mixture was stirred at room temperature for 18 hours. 1.9 g (10 mmol) of p-toluenesulphonic acid were then added and stirring was continued for 1 hour. The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel using ethyl acetate/dichloromethane (1:8) for the elution to give 24 mg (10%) of 3-methyl-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione in the form of a yellow solid of melting point 181°C.

The pentafluorophenyl pyruvate used as the starting material was prepared as follows:

736 mg (4 mmol) of pentafluorophenol and 825 mg (4 mmol) of dicyclohexylcarbodiimide were added to a stirred solution of 352 mg (4 mmol) of pyruvic acid in 10 ml of dichloromethane at 0°C under nitrogen. The mixture obtained was diluted with 40 ml of dichloromethane and stirred at room temperature for 18 hours. The solvent was removed under reduced pressure and the residue was treated with 5 ml of cold ethyl acetate. The mixture was filtered and the filtrate was evaporated to dryness. The residue as purified by flash chromatography on silica gel using ethyl acetate/dichloromethane (1:8) for the elution to give 802 mg of pentafluorophenyl pyruvate.

Example 20

In a manner analogous to that described in Example 1, 333 mg (1 mmol) of [8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indol-10-yl]glyoxylyl chloride were treated with 266 mg (1 mmol) of isopopyl 1-methyl-3-indoleacetimidate hydrochloride in different solvents and at various temperatures to give 3-[8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido [1,2-a]indol-10-yl]-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione. The results obtained are compiled in Table I:

Table I

Solvent	Temperature	Yield
Dichloromethane	0°C	228 mg (49%)
Dichloromethane	25°C	256 mg (55%)
Dichloromethane	40°C	269 mg (58%)
Dimethylformamide	25°C	195 mg (42%)
Ethyl acetate	25°C	312 mg (67%)
Dimethoxyethane	25°C	199 mg (43%)
Tetrahydrofuran	25°C	219 mg (47%)
Acetonitrile	25°C	162 mg (35%)
Dioxan	25°C	10 mg (2%)
Toluene	25°C	310mg (67%)

Table I (continued)

Solvent	Temperature	Yield
tert-Butyl methyl ether	25°C	157 mg (34%)

Example 21

In a manner analogous to that described in Example 1, 333 mg (1 mmol) of [8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indol-10-yl]glyoxylyl chloride were reacted with 266 mg (1 mmol) of isopropyl 1-methyl-3-indoleacetamidate hydrochloride using toluene as the solvent and different bases to give 3-[8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido-[1,2-a]indol-10-yl]-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione. The results are compiled in Table II.

Table II

Base	Yield
Dimethylaminopyridine	130 mg (28%)
Diisopropylethylamine	177 mg (38%)
Pyridine	87 mg (19%)
N-Ethylmorpholine	130 mg (28%)
DABCO	149 mg (32%)

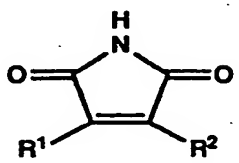
*DABCO = 1,4-diaminobicyclo[2,2,2]octane.

Example 22

A stirred solution of 2.43 g (10 mmol) of (S)-8-(acetoxymethyl)-6,7,8,9-tetrahydropyrido[1,2-a]indole (prepared as described in Example 2) in 15 ml of dichloromethane was treated at 0°C with a solution of 1.27 g (10 mmol) of oxalyl chloride in 5 ml of dichloromethane. The solution was stirred for 15 minutes and then treated with 2.67 g (10 mmol) of isopropyl 1-methyl-3-indoleacetimidate hydrochloride (prepared as described in Example 1) followed by 10 ml of dichloromethane. The mixture obtained was treated with 5.05 g (10 mmol) of triethylamine, allowed to warm to room temperature and stirred for 2 hours. The mixture was then washed with water and the organic layer was dried over magnesium sulphite and evaporated to dryness. The residue was dissolved in 30 ml of pyridine, cooled in ice and treated dropwise with 2.10 g (10 mmol) of trifluoroacetic anhydride over 2 - 3 minutes. After 15 minutes the solvent was evaporated in vacuo and the residue was partitioned between dichloromethane and 2M hydrochloric acid. The organic layer was washed with water and saturated sodium bicarbonate solution, dried over magnesium sulphite and evaporated. The residue was triturated with 30 ml of methanol and the solid was removed by filtration. The product was washed with methanol and dried to give 2.45 g (52%) of (S)-3-[8-(acetoxymethyl)-6,7,8,9-tetrahydro-pyrido[1,2-a]indol-10-yl]-4-(1-methyl-3-indolyl)-1H-pyrrole-2,5-dione in the form of a red solid of melting point 238-241°C.

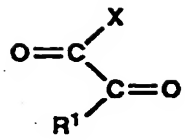
Claims

1. A process for the manufacture of substituted maleimides of the general formula



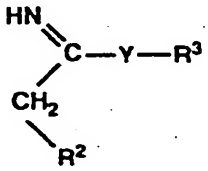
(I)

wherein R^1 represents alkyl, aryl or heteroaryl and R^2 represents hydrogen, alkyl, alkoxycarbonyl, aryl or heteroaryl,
which process comprises reacting an activated glyoxylate of the general formula



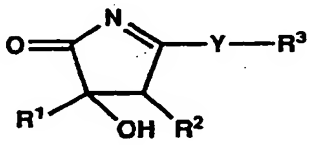
(II)

wherein R^1 has the significance given earlier and X represents a leaving atom or group, with an imidate of the general formula



(III)

wherein R^2 has the significance given earlier in this claim,
R^3 represents alkyl, aryl or trialkylsilyl and Y represents oxygen or sulphur,
in the presence of a base and, after treating a reaction product obtained in which R^2 represents hydrogen or alkyl with a strong base, hydrolyzing and dehydrating the resulting hydroxy-pyrrolinone of the general formula

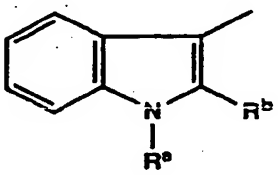


(IV)

wherein R^1, R^2, R^3 and Y have the significance given earlier in this claim.

2. A process according to claim 1, wherein an activated glyoxylate of formula II in which R^1 represents optionally substituted phenyl, naphthyl, thienyl, benzothiophenyl or indolyl is used.

3. A process according to claim 2, wherein R^1 represents a 3-indolyl group of the general formula



(a)

in which R^a represents alkyl or alkanoyl and R^b represents hydrogen or alkyl or R^a and R^b together represent a tetramethylene group optionally substituted by acyloxyalkyl.

4. A process according to claim 3, wherein R^a represents methyl or acetyl and R^b represents hydrogen or methyl or R^a and R^b together represent a tetramethylene group optionally substituted by acetoxymethyl.

5. A process according to any one of claims 1 to 4, wherein an activated glyoxylate of formula II in which X represents a halogen atom, particularly a chlorine atom, is used.

6. A process according to any one of claims 1 to 5, wherein an imidate of formula III in which R^2 represents optionally substituted indolyl, particularly 3-indolyl or 1-alkyl-3-indolyl, preferably 1-methyl-3-indolyl, is used.

7. A process according to any one of claims 1 to 6, wherein an imidate of formula III in which R^3 represents secondary alkyl, particularly isopropyl, is used.

8. A process according to any one of claims 1 to 7, wherein the reaction of an activated glyoxylate of formula II with an imidate of formula III is carried out in the presence of a tertiary amine or pyridine.

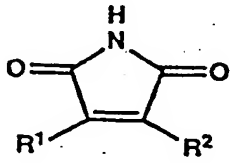
9. A process according to any one of claims 1 to 8, wherein a reaction product obtained in which R^2 represents hydrogen or alkyl is treated with an alkali metal alkoxide, particularly with potassium tert.butoxide.

10. A process according to any one of claims 1 to 9, wherein the hydrolysis and dehydration of a hydroxy-pyrrolinone of formula IV is carried out by treatment with a mineral acid or an organic acid, or by treatment with an acylating reagent in the presence of a base.

11. A process according to any one of claims 1 to 10, wherein the steps are carried out as a one-pot procedure.

Patentansprüche

1. Verfahren zur Herstellung substituierter Maleimide der allgemeinen Formel

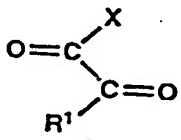


(I)

worin

R^1 Alkyl, Aryl oder Heteroaryl und
R^2 Wasserstoff, Alkyl, Alkoxycarbonyl, Aryl oder Heteroaryl bedeuten,

dadurch gekennzeichnet, dass es die folgenden Reaktionsschritte umfasst: Umsetzung eines aktivierten Glyoxylates der allgemeinen Formel

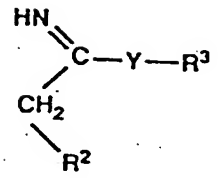


(II)

worin

R^1 die obige Bedeutung hat und
X ein Abgangs-atom oder eine Abgangs-gruppe darstellt,

mit einer Iminoverbindung der allgemeinen Formel

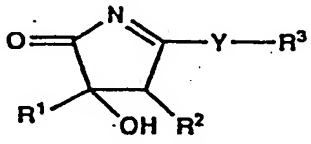


(III)

worin

R^2 die obige Bedeutung hat,
R^3 Alkyl, Aryl oder Trialkylsilyl und
Y Sauerstoff oder Schwefel darstellen,

in Gegenwart einer Base, und nach Behandlung eines erhaltenen Reaktionsproduktes, in dem R^2 Wasserstoff oder Alkyl bedeutet, mit einer starken Base Hydrolyse und Dehydratisierung des erhaltenen Hydroxypyrrolinons der allgemeinen Formel

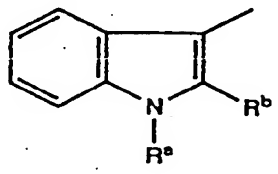


(IV)

worin R^1, R^2, R^3 und Y wie oben definiert sind.

2. Verfahren gemäss Anspruch 1, worin ein aktiviertes Glyoxylat der Formel II verwendet wird, in der R^1 gegebenenfalls substituiertes Phenyl, Naphthyl, Thienyl, Benzthiophenyl oder Indolyl darstellt.

3. Verfahren gemäss Anspruch 2, worin R^1 eine 3-Indolylgruppe der allgemeinen Formel



(a)

darstellt, in der

R^a Alkyl oder Alkanoyl und
R^b Wasserstoff oder Alkyl oder
R^a und R^b gemeinsam eine gegebenenfalls durch Acyloxyalkyl substituierte Tetramethylengruppe bedeuten.

4. Verfahren gemäss Anspruch 3, worin R^a Methyl oder Acetyl, R^b Wasserstoff oder Methyl oder R^a und R^b gemeinsam eine gegebenenfalls durch Acetoxymethyl substituierte Tetramethylengruppe darstellen.

5. Verfahren gemäss einem der Ansprüche 1-4, worin ein aktiviertes Glyoxylat der Formel II verwendet wird, in der X ein Halogen, insbesondere Chlor, darstellt.

6. Verfahren gemäss einem der Ansprüche 1-5, worin eine Iminoverbindung der Formel III verwendet wird, in der R^2 gegebenenfalls substituiertes Indolyl, insbesondere 3-Indolyl oder 1-Alkyl-3-indolyl, vorzugsweise 1-Methyl-3-indolyl bedeutet.

7. Verfahren gemäss einem der Ansprüche 1-6, worin eine Iminoverbindung der Formel III verwendet wird, in der R^3 sekundäres Alkyl, insbesondere Isopropyl, bedeutet.

8. Verfahren gemäss einem der Ansprüche 1-7, worin die Umsetzung eines aktivierten Glyoxylates der Formel II mit einer Iminoverbindung der Formel III in Gegenwart eines tert.-Amins oder von Pyridin stattfindet.

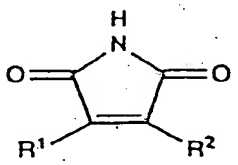
9. Verfahren gemäss einem der Ansprüche 1-8, in dem das erhaltene Reaktionsprodukt, in dem R^2 Wasserstoff oder Alkyl bedeutet, mit einem Alkalimetall-alkoxid, insbesondere Kalium-tert.-butoxid behandelt wird.

10. Verfahren gemäss einem der Ansprüche 1-9, worin die Hydrolyse und Dehydratisierung eines Hydroxypyrrolinons der Formel IV durch Behandlung mit einer Mineralsäure oder einer organischen Säure oder einem Acylierungsmittel in Gegenwart einer Base durchgeführt wird.

11. Verfahren gemäss einem der Ansprüche 1-10, worin die Umsetzungen in einem Eintopfverfahren erfolgen.

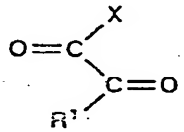
Revendications

1. Procédé pour la fabrication de maléimides substitués de formule générale



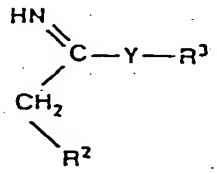
(I)

dans laquelle R^1 représente un groupe alkyle, aryle ou hétéroaryle et R^2 représente un atome d'hydrogène, un groupe alkyle, alcoxycarbonyle, aryle ou hétéroaryle,
ce procédé comprenant la réaction d'un glyoxylate activé de formule générale



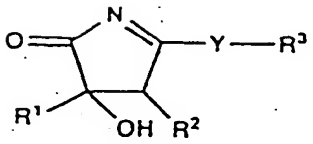
(II)

dans laquelle R^1 a la signification donnée plus haut et X représente un atome ou un groupe partant, avec un imidate de formule générale



(III)

dans laquelle R^2 a la signification donnée plus haut dans cette revendication, R^3 représente un groupe alkyle, aryle ou trialkylsilyle et Y représente un atome d'oxygène ou de soufre,
en présence d'une base et, après traitement d'un produit de réaction obtenu, dans lequel R^2 représente un atome d'hydrogène ou un groupe alkyle avec une base forte, hydrolyse et déshydratation de l'hydroxypyrrolinone résultante de formule générale

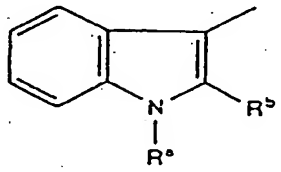


(IV)

dans laquelle R^1, R^2, R^3 et Y ont les significations données plus haut dans cette revendication.

2. Procédé selon la revendication 1, dans lequel on utilise un glyoxylate activé de formule II, dans laquelle R^1 représente un groupe phényle, naphtyle, thiényle, benzothiophényle ou indolyle, éventuellement substitué.

3. Procédé selon la revendication 2, dans lequel R^1 représente un groupe 3-indolyle de formule générale



(a)

dans laquelle R^a représente un groupe alkyle ou alcanoyle et R^b représente un atome d'hydrogène ou un groupe alkyle, ou bien R^a et R^b représentent ensemble un groupe tétraméthylène, éventuellement substitué par un groupe acyloxyalkyle.

4. Procédé selon la revendication 3, dans lequel R^a représente un groupe méthyle ou acétyle et R^b représente un atome d'hydrogène ou un groupe méthyle, ou bien R^a et R^b représentent ensemble un groupe tétraméthylène, éventuellement substitué par un groupe acétoxyméthyle.

5. Procédé selon l'une quelconque des revendications 1 à 4, dans lequel on utilise un glyoxylate activé de formule II, dans laquelle X représente un atome d'halogène, en particulier un atome de chlore.

6. Procédé selon l'une quelconque des revendications 1 à 5, dans lequel on utilise un imidate de formule III, dans laquelle R^2 représente un groupe indolyle éventuellement substitué, en particulier 3-indolyle ou 1-alkyl-3-indolyle, de préférence 1-méthyl-3-indolyle.

7. Procédé selon l'une quelconque des revendications 1 à 6, dans lequel on utilise un imidate de formule III, dans laquelle R^3 représente un groupe alkyle secondaire, en particulier isopropyle.

8. Procédé selon l'une quelconque des revendications 1 à 7, dans lequel la réaction d'un glyoxylate activé de formule II avec un imidate de formule III est réalisée en présence d'une amine tertiaire ou de pyridine.

9. Procédé selon l'une quelconque des revendications 1 à 8, dans lequel un produit de réaction obtenu, dans lequel R^2 représente un atome d'hydrogène ou un groupe alkyle, est traité avec un alcoxyde de métal alcalin, en particulier avec du t-butoxyde de potassium.

10. Procédé selon l'une quelconque des revendications 1 à 9, dans lequel l'hydrolyse et la déshydratation d'une hydroxypyrrolinone de formule IV est réalisée par traitement avec un acide minéral ou un acide organique, ou bien par traitement avec un réactif d'acylation en présence d'une base.

11. Procédé selon l'une quelconque des revendications 1 à 10, dans lequel les étapes sont réalisées selon un procédé en un réacteur.